Remarks and Arguments

Claims 62-63, 65-66, 70-73, 75-79, 82, 87-90, 99-100, 102-110, 113, 118-125, 131 and 133 are pending. Claims 62, 87, 88, 89, 90, 118, 119, 120, 131 and 133 are amended in response to the Examiner's comments. Applicants reserve the right to present additional subject matter in one or more continuation or divisional applications.

Rejection under 35 U.S.C. §112, first paragraph, enablement

Applicants were pleased to note that the Examiner has agreed that the specification enables claims reciting "the placement of a gene adjacent to an endogenous promoter, that the oocyte, two-cell embryo, or zygote are all enucleated, and that the surrogate mother is a suitable host for the animal to be grown to term." However, the Examiner continues to assert that the specification is not enabling for the breadth of modifying the nuclear genome of *any* somatic cell. The Examiner has acknowledged that the art recites using fibroblast or fibroblast-like cells.[1] Solely in the interest of promoting prosecution, Applicants have amended the claims to recite that cell in which a nuclear genome is modified is a "fibroblast-like" cell.

Rejection under 35 U.S.C. §112, second paragraph

Applicants were pleased to note that the Examiner has withdrawn the rejection under 35 U.S.C. §112, second paragraph of claims 62, 70, and 102 made in the previous Office Action. However, the Examiner has issued a new rejection of all pending claims under 35 U.S.C. §112, second paragraph as indefinite because independent claims 62, 90, and 133 recite both the terms "animal" and "mammal." Applicants have amended claims 62, 90, and 133 to recite only "mammal" throughout the claims. Applicants believe this amendment addresses the Examiner's rejection. However, should the Examiner's rejections on the above points remain as to the amended claims, she is asked to contact the undersigned to discuss appropriate amendments to clarify the subject matter.

Rejections under 35 U.S.C. §102(b)/103(a)

[1] The Examiner has noted that references Kalluri and Neison (2003), Chang (2002), Onishi (2000), Lai (2002) and Dai (2002) were not provided with the remarks. Although Applicants records indicate that several of these references are already of record, Applicants herewith attach another copy for the Examiner's files.

The Examiner has again rejected claims 62-63, 65-66, 75-76, 82, 87-90, 99-100, 106, 113, 118-122, 131 and 133 under 35 U.S.C §102(b) as anticipated or, alternatively, under 35 U.S.C. §103(a) as obvious over Campbell, et al. (WO 97/07669).[2]

The Examiner has asserted that that Campbell teaches methods of producing transgenic animals via nuclear transfer. Applicants do not dispute that Campbell was the first to prove that a viable animal could be developed from a somatic cell nucleus using nuclear transfer. But the present claims are not directed to the production of transgenic animals by nuclear transfer. Rather, the claims are directed to the production of transgenic animals by nuclear transfer where the donor nuclear genome has been modified at a targeted site. The claims very specifically recite that a nuclear genome is modified "at an endogenous locus by a genetic targeting event." This *is* the distinguishing feature.

Campbell notes that nuclear transfer is a step towards the successful generation of genetically modified animals. Applicants do not dispute that. What Applicants dispute is that Campbell taught anything of value, i.e., anything more than the prior art, as it relates to targeted genetic modification of donor nuclei.

As the Examiner has apparently acknowledged, it was accepted in the art, both before and after Campbell, that there were difficulties in targeting genetic events in somatic cells and thus these cells must be grown in culture for the significant time periods to identify a targeted modification. Therefore, the art recognized that targeted genetic modification *could not be used* in animals produced through nuclear transfer because the viability of the cells would be compromised by extended culturing. This is supported throughout the specification and the art. For example, as noted in the specification, it was well known that the ability to target a gene, *in contrast to randomly integrating it*, was much lower in somatic cells than in embryonic stem cells (see para 0117, also Arbones, et al. (1994) *Nat. Genet.* 6:90-97). It was also well known that primary cells have a lower frequency of homologous recombination than immortalized cells (see para 0118, also Finn, et al. (1989) *Mol. Cell. Biol.* 9:4009-4017 and Thyagarajan et al.

[2] Applicants have previously addressed this rejection, and have relied on certain references, notably Arbones (1994), Finn (1989), Thyagarajan (1996), Suraokar and Bradley (2000), and Porter (1997) in these arguments. The Examiner noted that these references were not submitted and therefore not considered in assessing the argument (see page 11 of the Office Action). Applicants note that, to the Applicants' knowledge, these references were previously included in the Information Disclosure Statement filed with this application on May 22, 2002. However, for the Examiner's convenience, the references are resubmitted herewith.

(1996) *Nuc. Acids Rsch.* 24:4084-4091). As noted in the declaration of Dr. Azim Surani, provided in the parent case US 09/475674 in 2001 and re-attached hereto, several factors, including the process of genomic imprinting were considered major obstacles to the use of genetically targeted somatic cells before the present filing. The art also recognized that targeting in somatic cells was not yet a realistic option (see, e.g. Porter, et al. (1997) *Transplant.* 64:1227-1235). Specifically, these authors note that "[m]ajor improvements in this and/or the efficiency of gene targeting itself will be required before the use of gene-targeted cells in autologous transplantation can be seriously contemplated" (page 1229).

This perceived difficulty in the prior art is highlighted in Suraokar and Bradley (2000) *Nature* 405:1004-1005, which is a comment on the scientific publication that embodied the present invention. In particular, Suraokar and Bradley comment on the contribution that the cloning of Dolly (i.e. the disclosure in Campbell) had on the possibility for making transgenic animals using nuclear transfer. As noted in Suraokar and Bradley, Campbell "revived" the hope that livestock could be genetically modified, *however,* the authors note that "[u]ntil now, no one had shown that it would be possible to specifically modify endogenous genes by cloning." Even shortly after the filing of the present case, authors such as Piedrahita note that available techniques were not likely to lead to targeted genetic modifications in somatic cells that could then be used for nuclear transfer, and that "in the future" techniques may be found for producing such targeted animals (see Piedrahita (2000) *Transgenic Research* 9:261–262). Until the date of the present invention therefore, skilled artisans were still looking for proof that the present invention of gene targeting and nuclear transfer "would be possible."

As the Examiner is aware, to be anticipating, a prior art reference must enable the claimed invention (see e.g. *Elan Pharms., Inc. v Mayo Found.*, 346 F.3d 1051 (Fed. Circ. 2003)). If the disclosure is merely a starting point for experimentation and a substantial uncertainty remains as to the success of the process, the reference is not anticipating (see e.g. *Dewey & Almy Chem. Co. v. Mimex Co.*, 124 F.2d 986 (2d Cir. 1942)). Campbell does not provide any techniques to overcome the art-recognized difficulties in developing targeted transgenic animals via nuclear transfer. Rather, Campbell broadly notes that "transgenic animals may be produced from genetically altered donor cells".... noting that "there are numerous techniques that can be used for genetically modifying cells" (see statements on pages 5-7 and 19-20 of Campbell). This is merely the expression of a hoped for result, offering nothing further regarding techniques or

inventive contributions that would have been considered clearly necessary by one of skill in the art to overcome the art recognized problem. Campbell provides nothing more than a starting point for experimentation and, given the art-recognized belief that somatic cells could not be useful in this process after targeting, substantial uncertainty remained that the process would be successful. Campbell is thus not enabled for the process recited in the claims and cannot destroy the novelty of the invention.

The Examiner has asserted that the methods steps recited in the claims are not distinguished from the teaching of Campbell and therefore if Campbell is not enabled, the claims are not enabled. Applicants strongly disagree. Unlike the present case, Campbell did not provide any process that included (a) modifying the nuclear genome of a fibroblast-like cell that has a sufficient lifespan to be useful for genetic modification, wherein the genome has a normal karyotype, at an endogenous locus by a genetic targeting event and then (b) transferring the modified nuclear genome to produce a viable nuclear transfer unit. Nothing in Campbell teaches that there even *is* a cell that would allow targeted genetic modification and subsequent nuclear transfer. Campbell merely provided a hoped for future result. Given the art-recognized problems associated with the process, and the belief that such a result was outside the realm of the existing techniques, there must be more than a mere broad brush stroke in a reference to enable it.

As nothing in Campbell provided one of skill in the art with a technique that would be expected to be useful without undue experimentation, Campbell does not destroy the novelty of the pending claims.

Non-obviousness

Campbell fails as a reference under 35 U.S.C. §103(a) for much the same reason as it fails under 35 U.S.C. §102. The reference simply provides no more than a hoped for result in a field in which the hoped for result was considered to be outside of the ability of the ordinarily skilled artisan.

As discussed above, because somatic cells have a limited lifespan in culture, their competence as nuclear donors was expected to decrease over time. Specifically, it was expected that prolonged culture required for selection of targeting events would cause detrimental changes in the somatic cell nucleus that would make any embryos derived from such cells non-viable.

Campbell merely shows that nuclear transfer could be successful from somatic cells but provides nothing to support using the process in a somatic cell that has been cultured for an extended period in vitro in order to obtain a targeted genetic modification and thus does not provide *any* expectation of success for of the fully scope of the present claims.

Moreover, as the Examiner is well aware, an "essential component" of the obviousness determination is the analysis of secondary indicia of non-obviousness (see *Graham v. John Deere Co. of Kan. City*, 383 U.S. 1), which include among others: a long felt need and failure of others, skepticism of skilled persons prior to the invention, commercial success and copying of the invention.

As evident from the cited references, including Campbell itself, the desirability of targeted genetically modified large animals was well established. However, as noted above, it is well documented that the skilled artisan, prior to the present filing, would have expected known techniques relating to targeted genetic modification to fail in the context of nuclear transfer, i.e., in the development of viable, genetically modified transgenic animals. Applicants note that even after Campbell's filing, it took over four years to develop the presently claimed techniques to produce viable, genetically targeted animals using somatic cell nuclear transfer.

Not only was there a long felt need for this invention and extensive skepticism and failure in the art, but to the Applicant's knowledge, *all* later authors publishing on genetically modified large animals have followed on the techniques described in the present application. Indeed, the paper in which the present invention was published -- in one of the world's premier scientific publications as McCreath, et al. (2000) *Nature* 405:1066-1069 -- has been cited at least 381 times by other scientific publications.

The long felt need to develop targeted genetically modified large animals, coupled with the lack of expectation of success using prior art techniques and the proven influence of the present invention in this field all support the non-obviousness of the present invention over Campbell.

The Examiner has also rejected claims 76-79, 107-110 and 12-124 under 35 U.S.C. §103(a) as obvious over Campbell in view of d'Apice, et al. (U.S. Patent No. 5,849,991) and claims 70, 73, 77, 102, 105, 107, 108 and 125 under 35 U.S.C.§103(a) over Campbell in view of Kucherlapati et al. (WO 94/02602). The Examiner asserts that Campbell is used to provide guidance to producing cloned, transgenic animals. As noted above, that is *not* the invention.

The invention is a method of providing cloned animals with a targeted genetic modification. This differs dramatically from the type of random integration that can produce a 'transgenic animal' without selection.

As noted above, Campbell does not anticipate or render obvious the claims because it provides merely a hoped for result with no proof that would have led a skilled artisan to believe that any available methods could overcome the art-recognized hurdles that led to an expectation of failure before the present invention.

Both d'Apice and Kucherlapati provide discussions focused on embryonic stem cell (ES) technology. The techniques used for ES technology are entirely inapplicable to the problem in the art as it relates to the present invention, i.e., the use of targeted genetic modification of somatic cells for nuclear transfer, because the low frequency of integration and extremely low rates of successful transfer that are found in nuclear transfer simply do not exist in ES technology. Since large animal ES cells were not available (and are still not available today), there is no additional teaching in d'Apice or Kucherlapati that would suggest that a technique had been developed to overcome the hurdles of associated with the use of targeted, genetically modified somatic cells as nuclear donors, nothing in the references remedies the deficiencies of Campbell.

The Examiner asserts that this argument fails because the claims are not limited to large animals. Applicants respectfully point out that the argument is as to the question of whether d'Apice or Kucherllapati provides any guidance in providing a targeted genetic modification of somatic cells in combination with nuclear transfer. Since the techniques of d'Apice and Kucherlapati are related to ES technology and *not* to somatic cell nuclear transfer, they do not.

The Examiner has also asserted that d'Apice is not relied upon with regard to producing animals by nuclear transfer, but only to provide motivation to provide a transgenic animal to reduce hyperacute rejection. Applicants note that the fact that a particular gene would be desirable is irrelevant when d'Apice does *nothing* to address the serious art-recognized problems associated with targeted genetic modification in combination with somatic cell nuclear transfer that are also not addressed by Campbell. In fact, D'Apice is relying on ES cell technology which to this day has not been enabled due to the lack of large animal ES cells. Therefore, a skilled artisan reading Campbell alone or in combination with d'Apice would not believe that a viable

animal with a targeted genetic event could be produced using the techniques as recited in the amended claims. Applicants respectfully request withdrawal of this rejection.

The Examiner has asserted two new grounds of rejection under 35 U.S.C. §103(a). The Examiner rejected claims 70, 72, 102 and 104 under 35 U.S.C. §103(a) as obvious in view of Campbell and U.S. Patent No. 6,013,857 ("the '857 patent"). The Examiner asserts that the '857 patent discusses producing transgenic bovines for producing recombinant milk and in particular, describes using endogenous milk promoter sequences. Applicants note that the '857 patent provides no more direction to making a targeted genetic modification using somatic cell nuclear transfer than any other reference cited. The entire patent is directed at using ES techniques or oocyte injection in cows and there is no exemplification of any other technique that would provide *any* additional motivation to one of skill in the art to achieve the claimed method. This is apparent in the abstract which cites that "[t]he method includes introducing the above transgene into an embryonal target cell of a bovine specie…" Much as with the other cited references, the '857 patent provides no additional guidance to overcome the art-recognized hurdle of somatic cell senescence in Campbell.

The Examiner has also rejected claims 70, 71, 102 and 103 under 35 U.S.C. §103(a) over Campbell in view of Bedalov (1994) *J. Biol. Chem.* 269:4903-4909 taken together with Rossert (1995) *J. Cell Biol.* 129:1421-1432. The Examiner asserts that Bedalov discusses the COL1A1 promoter fused to a reporter gene in a variety of mesenchymal cell types and that Rossert teaches that the precise sequences responsible for lineage specific expression had not been defined. Again, none of the additional references provide any teaching to address targeted gene modification and so would not alter the lack of expectation of success in the claimed techniques based on Campbell.

None of the cited references, alone or in combination overcome the art-recognized difficulties and lack of expectation of success in producing viable, genetically modified animals using somatic cell nuclear transfer. The present invention was the first in the world to produce such animals, which had long been desired but never made. Applicants respectfully request withdrawal of these rejections.

The fee for filing an RCE is included with this response. No further fees are thought to be required. However, the Commissioner is hereby authorized to charge any underpayment or credit any overpayment of fees to Deposit Account No. 11-0980.

Respectfully submitted,

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